May 24, 2007

David A. Neumann, Ph.D.
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Maryland Health Care Commission
4160 Patterson Avenue
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Re: Comments on draft regulations, COMAR 10.24.05, Research Waiver Applications for Participation in the Atlantic Cardiovascular Patients Outcomes Research Team (C-PORT) Study of Percutaneous Coronary Interventions Performed in Maryland Hospitals without On-Site Cardiac Surgery.

Dear Dr. Neumann:

The C-PORT protocol is a randomized non-inferiority study of elective percutaneous coronary intervention (PCI) comparing outcomes in patients entering hospitals without on-site surgery (non-SOS) treated at the non-SOS hospital or referred to a SOS hospital in a 3 to 1 ratio. The C-PORT investigators have declared two primary endpoints, mortality at 6 weeks and MACE at 9 months. Investigators hope that results of the trial will assist policy makers in deciding whether the current State of Maryland policy of restricting elective PCI to hospitals with SOS should be maintained or changed to a less restrictive approach.

The sample size goal is 18,360 and has 80% power to detect a 50% increase in an anticipated SOS hospital six week mortality rate (0.8%) compared with a non-SOS hospitals mortality rate (1.2%) with less than a 5% probability that the result is due to the play of chance. The investigators believe that the sample size can be reached with 40 centers randomizing 200 patients per year and this at full speed would generate the sample size within 28 months.

Suburban believes that the question is important and that the protocol is well designed. The problem, as with all clinical trials, will lie in execution. It is quite likely that the recruitment of hospitals and patients will be slow and gathering accurate data in a timely fashion will be critical. The Maryland Health Care Commission and staff should consider establishing their own dedicated Data Monitoring Committee to preclude a nasty surprise of slow recruitment and data that are incomplete or inaccurate.

The following list of potential difficulties should be considered by the Commission in monitoring the trial/investigator performance:

1. **The sample size is enormous.** For the 40 anticipated sites, it would require 4 patients to be randomized each and every week for 28 months. Sites accepted into clinical trials vary and some of those chosen will not be able to deliver at this level requiring either additional sites or existing sites to perform at an increased rate or over a prolonged period of recruitment. **Reduction in sample size achieved will reduce the power of the trial to detect a 50% increase in mortality – potentially leading to a false conclusion of no difference when in fact one exists.**
2. In the event that the sample size is reached, variation across sites in expertise and number of patients randomized could generate a result dominated by a few sites that were able to recruit well, leaving policy formulation for all sites wishing to do elective PCI in a quandary.
3. Informed consent in this trial will be sought from large numbers of vulnerable patients, those with acute frightening illnesses such as unstable angina or non-ST elevation infarction. Further, many of these patients are likely to have more complex anatomy than patients undergoing primary angioplasty. Investigators will be under pressure from Dr. Aversano and hospital executives to enter large numbers of patients particularly when the hospital is not meeting recruitment goals. This may tempt some to be less informative during the informed consent discussion or to agree with the patient who says "do what you think is right, doctor" and proceed without full disclosure. It would be interesting to know how many of the C-PORT investigators have actual clinical trial experience and are attuned to the importance of truly informed consent.
4. Most sites will, by definition, be low volume sites and the risks that patients take when they agree to randomization are not well understood. When time to balloon inflation is less important, as in elective PCI, many patients might well choose to transfer to a high volume site since by virtue of the current state requirements all SOS centers are higher volume PCI sites.
5. Careful application of inclusion and exclusion criteria should be monitored carefully. Pressures to enter patients and to provide excellent results push in opposite directions (enter as many as possible or select only very low risk patients) and it is difficult to predict which tendency will predominate. It is essential to gather some data on those who refuse randomization and those who were not asked to participate.
6. Follow-up will be difficult particularly in those patients randomized to SOS hospitals since no staff/patient relationship will be built in a short stay in the non-SOS hospital.
7. The longer the trial takes to reach the sample size the less homogeneous the patients included in the study will be by virtue of advances in diagnostic and therapeutic strategies. **A major concern will be what to do with 3 or 4 years**

elapsed and a sample size of 8000. Investigator fatigue will also be a problem should this delay occur.

8. The State should consider establishing its own data monitoring committee to assess performance and, if needed, outcomes. The State has a stake in good performance and should have advice from an independent group of experts. This is particularly true should recruitment falter or data collection be less than complete. Failure to attain sample size or collect accurate data puts patients at research risk without the desired outcome of conclusive scientific results.

I hope you find these comments helpful.

Brain Gragnolati
President and CEO